REMARKS

A. Status of the Claims

Claims 29-47 are pending in the application, claims 1-28 and 48 having been canceled previously. Claims 29-47 are rejected under 35 U.S.C. §112, first paragraph, claims 29, 31, 32, 41 and 45 are rejected under 35 U.S.C. §102(a), and claims 30, 33-40 and 42-44 are rejected under 35 U.S.C. §103(a). The specific grounds for rejection, and applicants' responses thereto, are set out in detail below.

B. Rejections under 35 U.S.C. §112, First Paragraph

The examiner continues to reject the present claims as not enabled, arguing that the specification fails to "show a correlation between that which occurred *in vitro* to that which one of skill in the art would reasonably expect *in vivo*." The examiner also cites genomic diversity, cell free transmission, latency, CNS "depot" effects, and complexity and variation of the disease as obstacles that preclude a presumption of enablement. Further, references are said to teach problems and failure *in vivo*.

With regard to the first issue, applicants now present data recently obtained using both *in vitro* and *in vivo* models of HIV infection. An *in vitro* study was performed where PMBCs from three chimpanzees were infected with HIV-1 IIIB. Low levels of infection were established in these cells. Administration of R15K peptide to the PMBCs inhibited this low level of infection altogether, confirming experiments performed previously.

In vivo experiments involved infection of the same three animals with HIV-1 IIIB. Two of the animals were treated with R15K peptide, each receiving a total of 8 injections by intravenous infusion over a 28-day period. The third animal served as a negative control and did not receive any R15K. Virus titer was monitored at various time points using quantitative PCR™.

For the two chimpanzees treated with R15K peptide, 4 of 7 samples taken during the 28-day treatment period were negative for virus, while the other 3 samples were positive, but only at low levels. Scoring degree of positive per sample gives a value of 0.43. On the other hand, for the negative control animal, out of a total of 4 samples examined, 3 showed positive counts with two showing substantial amounts of virus. Again, degree of positive per sample gives a value of 1.38, more than triple that of the treated animals.

These results suggest that the R15K peptide inhibits HIV replication both *in vitro* and *in vivo* in chimpanzees. It is known that HIV-replication exhibits periodicity in chimpanzees, which is reflected by the variability in results for a given animal. However, the overall titers during the test period clearly were higher in the untreated animal, as compared to the R15K-treated animals.

Applicants submit that, even in light of the citations advanced by the examiner, there is strong evidence that indicates a reduction of HIV-replication *in vitro* correlates with that observed *in vivo*. This is *prima facie* evidence of enablement, and addresses one of the examiner's major concerns.

As for the listing of "obstacles," applicants respectfully submit that each of these points was dealt with in the first response. These are repeated below for the examiner's convenience:

> Moving on to the other issues, it would appear to reduce to, essentially, two concerns. One basic concern is that the virus will somehow physically evade the effects of a therapeutic agent, for example, by remaining hidden inside cells in a latent state or in a covert form, through virus-free or direct cell-to-cell transmission, or by taking refuge in CNS cells. The other concern is that the virus will genetically evade the therapeutic agent, for example, by mutating its genome. (Footnote 1: The other stated concern, that the disease is complex and variable, seems to be more a statement of fact than a particular reason why this very specific claim would not be enabled. Such general observations fail to highlight any perceived defect in the claims.) However, neither of these concerns gives rise to a significant enablement issue for the present claims, as explained below.
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> Again, applicants refer to the amended claim language which specifically recites the provision of a certain peptide to a cell, whereby the peptide directly blocks the entry of HIV into the cell. The concerns stated above, even if taken as true, would not preclude the present invention from being practiced effectively by the skilled artisan. For example, it is well known that, despite the alternative modes for viral transmission, free infectious virus is found in HIV patients and that this virus infects healthy target cells. See, for example, Wei *et al.*, *Nature* **373**:117-122 (1995); Ho *et al.*, *Nature* **373**:123-126 (1995); Perelson *et al.*, **271**:1582-86 (1996). The ability of the claimed peptides to inhibit infection of cells by HIV has not been effectively challenged. Also, it is important to remember that applicants do not claim a cure for HIV but, rather, a method of inhibiting the progression of the disease by virtue of blocking ***one*** of the modes of virus transmission. It is ***this*** invention that is at issue, not one of disease cure by immunologic means.
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> While it is true that HIV does undergo remarkable changes in its structure in a human subject, and that many of these changes are found in the gp120 *env* product. The V3 loop sequences of the present claims represent a common sequence motif from that region of gp120, however, and despite (i) the fact that not all HIV strains will have this sequence, and (ii) the fact that a given virus ***may*** mutate to lose this sequence, there remain a large number of AIDS victims that are infected by a virus having precisely the V3 loop sequences set forth in the claims. Thus, for these patients, the present invention will prove effective at limiting the extent of (not preventing all) viral infection.
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> This phenomenon further is elucidated in the attached manuscript by Nehete *et al.* This paper describes studies which confirm the present invention by demonstrating the ability of V3 loop peptides to inhibit infection. Interestingly, these V3 loop peptides bind to target cells and are competed with by viral particles, ***but not*** recombinant gp120, sCD4, β-chemokines or antibody to CXCR-4. This difference in competition correlates well with the fact that while many other candidate molecules ***cannot*** effectively inhibit infection, V3 loop peptides can.

Thus, the remaining issues argued by the examiner have been addressed.

In sum, applicants respectfully submit that the present invention, by virtue of its unique mode of action, provides improved methods that avoid the problems noted by the examiner. Furthermore, the present invention need not be flawless in order for the skilled artisan to utilize it, and thus should be patentable even in the face of possible remaining problems. Reconsideration and withdrawal of the rejection is respectfully requested.

C. Rejections under 35 U.S.C. §102 (a)

Claims 29, 31, 32, 41 and 45 are rejected, under 35 U.S.C. §102(a), as anticipated by Berzofsky *et al.* The examiner again asserts that Berzofsky discloses a method for protecting cells from HIV comprising administering to mice a composition which comprises a peptide having the claimed sequence, and restimulating the cells again be contacting the cells *in vitro* with the composition. Applicants respectfully traverse this rejection.

Applicants acknowledge that the goal of both the instant application and Berzofsky is the protection of cells from HIV. Applicants further acknowledge that both the instant application and Berzofsky rely upon a peptide, designated as R15K. However, the mechanisms of protection sought by the instant application, and its particular use, are quite distinct from Berzofsky.

The protection described in Berzofsky is established by the administration of the peptide to a naïve host. Cells within the host take up the peptide, process the peptide within the

endoplasmic reticulum where the peptide is associated with MHC class I. The peptide/MHC complex is then surface expressed by the cell. Naïve cytotoxic T lymphocytes (CTL) that possess the proper TCR configuration recognize the peptide as foreign, become activated and proliferate, creating a subpopulation of anti-gp120 peptide CTL. In the event of a viral infection, this subpopulation can rapidly expand to kill cells infected with the virus. Cells expressing the viral peptide on their surface are recognized by the CTL subpopulation and either lysed or induced into an apototic state. By eliminating these infected cells, the production of viral particles is curtailed and, ideally, the infection eventually is curtailed or terminated.

In contrast, the instant application envisions the inhibition of viral uptake through the direct interaction between the claimed peptides and the virus or target cells. Upon administration to a host, the peptide itself inhibits the entry of the viral particle by directly preventing the interaction between the virion and the cell. The instant application is not directed towards employing the peptide to elicit an immune response; rather the claimed peptide itself directly inhibits the interaction required for the virion to enter the target cell. The fact that the peptide inhibits viral entry rather than a cellular response elicited by the peptide distinguishes the instant application from the cited prior art.

The Federal Circuit has determined that, to support a §102 rejection, the cited prior art reference must contain each limitation of the anticipated claim and enable one skilled in the art to make the anticipated subject matter. *Chester v. Miller*, 906 F.2d 1574, 1576 n.2, 15 U.S.P.Q.2d 1333, 1336 n.2 (Fed. Cir. 1990). Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not sufficiently enabling. *In*

re Borst, 345 F.2d 851, 855, 145 U.S.P.Q. 554, 557 (C.C.P.A. 1965), cert. denied, 382 U.S. 973, 86 S.Ct. 537, 15 L.Ed.2d 465 (1966). The phrase "for directly inhibiting HIV entry into cells" in the claims of the instant application envisions a method in which the cells to be protected are contacted with a preparation which, itself, directly inhibits the ability of viral particles to infect the cell. Such a term, even though it appears in the preamble to the claim may be deemed a limitation of the claim when it gives meaning to the claim and properly define the invention. *In re Paulsen*, 30 F.3d 1475, 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994). The claim language of the instant application thus specifically envisions that the inhibition of viral entry results from the peptide itself, rather than a response generated as a result of previous administration of the peptide.

The examiner may, alternatively, be basing her rejection on the doctrine of inherent anticipation. While it is arguable that the method taught by the Berzofsky *et al.* patent could result in collateral inhibition of viral uptake by direct peptide interaction, this is not what is taught by the patent, nor what was envisioned by the inventor. The patent teaches a method of inducing a CTL response, and one of ordinary skill in the art would not derive from its teachings a means of directly inhibiting viral uptake. It further would be recognized that the methods and means necessary to initiate an immune response differ from the methods and means necessary to directly inhibit viral entry.

Anticipation by inherency requires that 1) the missing descriptive matter be necessarily present in the prior art reference and that 2) it would be so recognized by persons of ordinary skill in the art. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d

1746, 1749 (Fed. Cir. 1991). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Hansgirg v. Kemmer*, 102 F.2d 212, 40 U.S.P.Q. 665, 667 (CCPA 1939). The Berzofsky patent fails to provide any teaching that the processes disclosed therein would result in anything more than the initiation of an immune response against viral antigens. One of ordinary skill would not extrapolate from the reference that the method might be used for the additional purpose of directly inhibiting viral entry.

The teachings of the cited reference fail to expressly or inherently anticipate the subject matter of the instant application. However, in the interest of advancing the prosecution, applicants have amended the claims such that the claims are directed to (a) human treatment (claim 29) or (b) *in vitro* treatment (claim 48). Claim 46, drawn to human treatment, has previously been indicated as free of the art. Claims to *in vitro* treatment are novel and non-obvious over references addressing immunologic methods. In view of all the preceding, it is respectfully requested that the examiner remove the rejections asserted against the application under 35 U.S.C. §102(a).

D. Rejections under 35 U.S.C. §103(a)

The examiner rejects claims 30, 33-40 and 42-44 under 35 U.S.C. §103(a) as being unpatentable over Berzofsky *et al.* in view of Haynes *et al.* The teachings of the Berzofsky patent have been previously discussed. Haynes *et al.* is asserted to disclose methods of protecting animals against HIV comprising administering peptides which are similar to the claimed sequences and that these peptides inhibit syncytia formation. The reference further asserted to teach that the peptide may contain one or more sequences from different or the same

isolate which can be linked via cysteine and may include a spacer. Applicants respectfully traverse this rejection.

Haynes *et al.* and Berzofsky *et al.* each relate to the use of peptides to initiate an immune response to HIV. As discussed, the claims of the instant application, in contrast, relate to the inhibition of viral uptake by target cells directly through their interaction with the peptide. The peptide itself inhibits the interaction between the virion and target cell necessary for viral uptake to occur. Elicitation of an immune response is not envisioned nor sought by the inventors of the instant application.

The examiner states that the use of the peptide to inhibit syncytia formation in the Haynes *et al.* patent, when combined with Berzofsky *et al.*, would render claims 30, 33-40 and 42-44 obvious. It appears that the examiner is mistaken in interpreting Haynes *et al.* The method by which syncytia are inhibited in Haynes *et al.* is through the use of antibody raised against the viral peptides (page 10 lines 14-25). While the peptide was initially employed to stimulate production of these antibodies, it is not the peptide itself that is inhibiting syncytia formation; rather it is the antibody raised against the peptide. These antibodies are not equivalent to the peptides initially introduced to produce the antibodies nor the peptides envisioned in the instant application to inhibit viral entry.

The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that a claimed process should be carried out and would have a reasonable likelihood of success viewed in the light of the prior art.

University of California v. Synbiotics Corp., 29 U.S.P.Q.2d 1955, 1956 (Cal. 1993). Further, the pertinent comparison upon which an obviousness rejection is based must involve an evaluation of the invention as a whole in light of the prior art as a whole. *In re Langer and Haynes*, 465 F.2d 896, 175 U.S.P.Q. 169, 171 (C.C.P.A. 1972). The combination of the cited prior art would not suggest to one of ordinary skill a method of directly inhibiting viral entry into a cell by directly contacting the virus or target cell with the peptide. Each reference relates to eliciting an immune response rather than directly inhibiting viral entry. The fact that the Haynes art discloses peptide conjugates does not provide elements related to the direct inhibition of viral uptake, and thus fails to provide any indication that one of ordinary skill would have a reasonable likelihood of success in carrying out the invention as claimed in the instant application.

The combination of the cited references would not suggest to one of ordinary skill in the art that the claimed process should be carried out or that there would be a reasonable likelihood of success in practicing the claimed invention. However, in the interest of advancing the prosecution, applicants have amended the claims such that the claims are directed to (a) human treatment (claim 29) or (b) *in vitro* treatment (claim 49). Claim 46, drawn to human treatment, has previously been indicated as free of the art. Claims to *in vitro* treatment are novel and non-obvious over references addressing immunologic methods. In view of the preceding, it is respectfully requested that the examiner remove the rejections asserted against the application under 35 U.S.C. §103.

E. Summary

In light of the preceding remarks, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the attorney at 512-418-3184 is invited.

Respectfully submitted,

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